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КОРЬ. КРАСНУХА. СКАРЛАТИНА

MEASLES. RUBELLA. SCARLET FEVER

Учебно-методическое пособие

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ABBREVIATIONS

AME — acute measles encephalitis

APME — acute postinfectious measles encephalitis

ARF — acute rheumatic fever

CBC — complete blood count

CNS — central nervous system

CRI — congenital rubella infection

CRS — congenital rubella syndrome

CSF — cerebrospinal fluid

ECG — electrocardiogram

EEG — electroencephalogram

EIA — enzyme immunoassay

ELISA — enzyme-linked immunosorbent assay

ESR — erythrocyte sedimentation rate

GAS — group A streptococci

HIV — human immunodeficiency virus

HNIG — normal human immunoglobulin

MMR — measles, mumps, and rubella

MMRV — measles, mumps, rubella, and varicella

RBCs — red blood cells

RV — rubella virus

RT-PCR — reverse transcription polymerase chain reaction

SpeB — streptococcal pyrogenic exotoxin B

SSPE — subacute sclerosing panencephalitis

WBCs — white blood cells

MOTIVATIONAL CHARACTERISTICS OF TOPIC

Total in-class hours – 4.5.

Measles and rubella are one of the most frequent infectious diseases of childhood, characterized by the appearance of exanthema. High infectivity, severity, the development of various complications require doctor's knowledge of the

clinical features of these diseases, the ability to make the differential diagnosis between them and other diseases which are accompanied by exanthema. The correct and timely diagnosis, adequate treatment allow, in most cases, to avoid unwanted effects, to prevent the development of life-threatening complications and morbidity in children's groups.

Since the mid 80-ies streptococcal infection has been developing, similar to the one that raged in the early 20th century. The specific feature of modern strains of Group A Streptococcus lies in their ability to cause severe invasive infection. Both adults and children can have invasive forms of streptococcal infection. Moreover, it does not depend on the initial immune status of the person. In addition, strains of Streptococcus, which often lead to the development of autoimmune complications started to circulate.

Scarlet fever, as one of the manifestations of Group A Streptococcal infection, tends to aggravate the clinical manifestations of the disease, causes more frequent complications, some of which can be fatal. The outcome of streptococcal infection is largely dependent on the knowledge of the primary care provider in the area of recent clinical features and management of streptococcal infections.

The objective of the lesson. The purpose of teaching and learning consists in the formation of obtaining and getting to the student scientific knowledge about modern diagnosis, treatment and prevention of measles, rubella and scarlet fever, taking into accounts the features of the clinical course of the disease, depending on the child's age and reactivity.

Class tasks. The students should know:

– etiology, epidemiology, classification, pathogenesis, clinical symptoms and syndromes of measles, rubella, scarlet fever in children and adolescents;

– clinical and epidemiological directions, rules of hospitalization of children with measles, rubella, scarlet fever and epidemiological regime (inpatient and outpatient);

– specificity of laboratory diagnosis of measles, rubella, scarlet fever and differential diagnostics with other diseases that have similar clinical picture;

– main complications and outcomes of measles, rubella, scarlet fever, the principles of treatment of children with these diseases;

– clinical symptoms and special characteristics of emergency conditions in children and adolescents with measles, rubella and Group A Streptococcal infection;

– the principles and methods of general and special prevention of measles, rubella, scarlet fever; vaccination calendar and organization of outpatient immunoprophylaxis.

The students should be able to:

– perform clinical examination of a child with measles, rubella, scarlet fever, make the plan of examination, identify the need for hospitalzation of a child with these infection;

– evaluate the results of examination of patients with measles, rubella, scarlet fever, deliver a clinical diagnosis;

– fill in medical documents in cases of measles, rubella, scarlet fever;

– organize preventive measures at the site of infection.

The students should master:

– methods of epidemiological analysis of development of measles, rubella, scarlet fever in children;

– methods of identifying the clinical symptoms, atypical, severe and complicated forms of infections;

– contemporary methods of clinical, instrumental and laboratory examination, methods of inpatient and outpatient giving first medical aid in life- threatening conditions;

– methods of treatment and rehabilitation of recovering children with measles, rubella, scarlet fever;

– methods and form of sanitary education of the population.

Requirements for the initial level of knowledge. Revise:

– Human Anatomy — anatomical and morphological structure of the skin;

– Microbiology, Virology, Immunology — characteristics of measles and rubella viruses, fundamentals of immunity; classification of streptococci, their role in human pathology; characteristics of Group A Streptococcus;

– Pathologic Physiology — patterns of occurrence and mechanisms of the development of pathological processes in the skin and mucous membranes with infectious exanthema;

– Biological Chemistry — molecular basis of development of pathological processes, basic principles of biochemical diagnostic methods;

– Propedeutics of Internal Diseases — examination approaches, clinical and laboratory parameters evaluation;

– Neurology and Neurosurgery — examination methods in neurology and neurosurgery.

Questions for self-control from related disciplines.

1. Give a description and name the main properties of the measles virus.

2. Give a description and name the main properties of rubella virus.

3. What are the primary and secondary elements of rash? Give their description.

4. What are the pathological changes in the skin and mucous membranes in case of infectious rash?

5. What clinical and laboratory techniques of examination do you know?

6. How are streptococci divided in relation to blood agar?

7. What streptococci most frequently cause disease in humans?

8. Give a description and name the main properties of Group A Streptococcus.

9. What morphological changes in the myocardium are defined in the heart of patients with scarlet fever (acute rheumatic fever)?

10. What are the serological markers of acute rheumatic fever? Can they be used for the diagnosis of streptococcal infection?

Test questions on the topic of the lesson.

1. Give a description of the main stages of epidemic process in measles and rubella.
2. List the terms of incubation period in measles and rubella, scarlet fever. What does it depend on?
3. Give the clinical characteristic of the periods of measles.
4. What is the classification of rubella. Give the clinical characteristic of its different forms.
5. Give a description of diagnostic methods of measles, rubella detection**.**
6. List the indications for hospitalization and the principles of treating patients with exanthemas.
7. What kinds of infectious exanthemas may occur as a congenital infection?
8. What are the complications of measles, rubella and the time of their appearance.
9. Differential diagnosis of measles and rubella.
10. What are the conditions for discharge from hospital and return to the children's groups after measles, rubella and scarlet fever?
11. What is the causative agent of scarlet fever; specify its main properties.
12. Specify the source, modes of transmission of infection.
13. What is the classification of scarlet fever.
14. Why does β-hemolytic group A Streptococcus cause various infectious and non-infectious diseases?
15. Give a description of the atypical forms of scarlet fever, measles, rubella.
16. What is an «invasive» streptococcal infection? Give its clinical characteristics.
17. What are the complications of scarlet fever? How are they subdivided and clinically manifested; the time of its appearance.
18. What are the typical changes in scarlet fever laboratory data?
19. Make the differential diagnosis of scarlet fever.
20. What is the duration of etiotropic therapy in streptococcal infection. What antibiotics should be chosen? How do we apply them?
21. Indications for hospitalization of patients with scarlet fever. The rules of locating the patients in the wards.
22. What preventive and anti-epidemic measures should be carried out in sites of measles, rubella and scarlet fever?

MEASLES

Measles (also known as rubeola or morbilly) is one of the most contagious infectious diseases characterized by rash, fever and respiratory symptoms. It is a viral infection with a substantial degree of morbidity and significant mortality. Despite being considered primarily a childhood illness, measles can affect people of different ages.

HISTORICAL BACKGROUND

Historically epidemics of measles have been huge killers of children and have been known to change the course of history. Before an effective vaccine became available, was an inevitable step in human development.

Global vaccination programs had reduced the number of deaths from measles (figure 1A). Unfortunately, due to different vaccination problems today measles remains a common disease in many parts of the world, including Europe, the Middle East, Asia, the Pacific, and Africa. Today measles is one of the leading vaccine-preventable disease causes of death. Most of those who die from the infection are less than five years old.

Measles continues to spread across Europe because vaccination coverage in many countries is suboptimal. Vaccination coverage of at least 95 % for both the first and second doses of measles-containing vaccine must be achieved at all subnational levels and in all communities to interrupt measles circulation.

ETIOLOGY

The disease is caused by Measles morbillivirus.Virus classification: Rigavirales → Paramyxoviridae → Orthoparamyxovirinae → Morbillivirus → Measles morbillivirus.

It is a single-stranded, negative-sense, enveloped RNA virus (ssRNA) meaning it first has to be transcribed by RNA polymerase into a positive-sense messenger RNA strand.

The measles virus has two envelope glycoproteins on the viral surface — hemagglutinin (H) and membrane fusion protein (F). These proteins are responsible for host cell binding and invasion.

The genome of measles virus is about 16, 000 nucleotides encodes, six structural proteins, the nucleoprotein, phosphoprotein, matrix, fusion, haemagglutinin, and large protein, and two non-structural proteins V and C encoded within the phosphoprotein gene. The haemagglutinin protein is one of two transmembrane glycoproteins on the surface of the virion and binds to cellular receptors, including the signalling lymphocyte activation molecule (SLAM or CD150) on lymphocytes, monocytes, macrophages, and dendritic cells, and nectin-4, a component of epithelial cell adherens junctions.

The distribution of these receptors determines the broad cell types and tissues infected with measles virus. The lifelong immunity that follows measles is due to neutralising IgG antibodies to the haemagglutinin protein that block binding to host cell receptors.

The fusion protein, the second viral glycoprotein exposed on the viral surface, is responsible for fusion of the viral envelope with the host cell membrane, enabling entry of viral ribonucleoproteins into the cell cytoplasm.

Today 24 genotype reference strains are recognised by WHO, but only eight of them have been detected since 2009, suggesting many genotypes are no longer circulating.

Genetic characterisation of circulating wildtype measles virus is important in transmission pathways, distinguishing endemic from imported strains, and number of measles cases notified. The major genotypes differ between countries and status of measles circulation within that country or region. Genotyping can also differentiate vaccine from wildtype measles virus, which is important in assessing vaccine-associated adverse events.

Despite the variety of measles genotypes, there is only one measles serotype. Antibodies to measles bind to the haemagluttinin protein. Therefore, antibodies against one genotype (such as the vaccine strain) are protective against all other genotypes.

EPIDEMIOLOGY

Humans are the only natural hosts of the virus, and no other animal reservoirs are known to exist. Wildtype measles virus is pathogenic only for primates. The virus is highly infectious.

In temperate areas, it usually causes disease in late winter and early spring, whereas, in the tropics, it is commonest in the dry season.Where infection is frequent, epidemics occur every 2 years.

In the pre-vaccination era, >90 % of individuals had a symptomatic infection by the age of 10 years.

WHO estimates that due to vaccination worldwide deaths fell from 562, 000 in 2000 to 89, 780 in 2016, but in 2017 it increased to 110, 000.

The overwhelming majority of measles and measles deaths occur predominantly in areas with low vaccination rates, low per capita incomes and weak health infrastructures particularly in the developing world, especially in parts of Africa and Asia (table 1).

Table 1

World distribution of measles cases in 2018

WHO Region	Total measles	Clinically confirmed	Laboratory-confirmed
African Region	54740	16345	7524
Region of the Americas	16615	0	16615
Eastern Mediterranean Region	57054	29535	11964
European Region	83103	50946	27983
South-East Asia Region	82384	57299	7149
Western Pacific Region	30381	18290	10349
Total	**324277**	**172415**	**81584**

However, last years measles has rebounded in the WHO's 53-nation European Region, threatening efforts to eliminate the disease. Following a record low of 5,273 cases in 2016, a total of 21,315 cases were recorded in 2017. This included 35 deaths. In 2018 the World Health Organization reported about more than 80 000 people in 47 of 53 European countries contracted measles (61 % hospitalised) and 72 deaths. The highest number of cases were reported by France (2 800), Italy

(2 632), Greece (1 862), Romania (1 247), United Kingdom (941), Slovakia (614) and Germany (516). Notification rates per million population above the EU/EEA average (23.7) were reported by Greece (172.9), Slovakia (113.0), Romania (63.5), Italy (43.4) and France (41.8).

Despite more children in the WHO European region being vaccinated against the disease than ever before, progress on vaccination is uneven between and within countries. This leaves clusters of susceptible people unprotected, particularly in middle income countries. Ukraine had an incidence rate of 1209 per 1 million population and 53 218 cases; Serbia had a rate of 579 and 5076 cases; Georgia had a rate of 563 and 2203 cases; and Albania a rate of 499 and 1466 cases.

WHO urged affected countries to target their interventions to places and groups where immunisation gaps persist.

Although measles was eliminated from the United States in 2000, it still occurs following measles virus importations from other countries, most commonly by unvaccinated US residents who become infected while traveling abroad. In recent years, the annual number of reported measles cases in the United States has increased and larger outbreaks have occurred, predominantly among persons who are unvaccinated by choice.

From January 1 to March 28, 2019, 387 individual cases of measles have been confirmed (372 in 2018 totally) in 15 states. This is the second-greatest number of cases reported in the U.S. since measles was eliminated in this region.

PATHOGENESIS

Transmission. Measles is an airborne disease which spreads easily via respiratory droplets and aerosolised particles (through the coughs and sneezes of infected people), which may persist in the air for several hours (figure 1). It has been speculated that infection of epithelial cells during the late stage of measles pathogenesis may contribute to measles virus transmission.

It may also be spread through contact with saliva or nasal secretions. Highly infectious, up to 90 % of not immune contacts are infected. One contagious individual can infect for 9–18 susceptible persons (figure 1B).

Virus can survive on surfaces for up to 2 hours, but it’s lipid envelope is destroyed by ethanol-based handscrubs.

The period of infectiousness is from 4–5 days before to 4 days after the start of the rash.

Measles can have regular temporal patterns, driven by the accumulation and decline of susceptible individuals, and cluster spatially among susceptible populations.

Incubation period is from 6 to 19 days (median 13 days) with a range up to 23 days in some cases (figure 1B). The virus replicates and spreads during the incubation period.

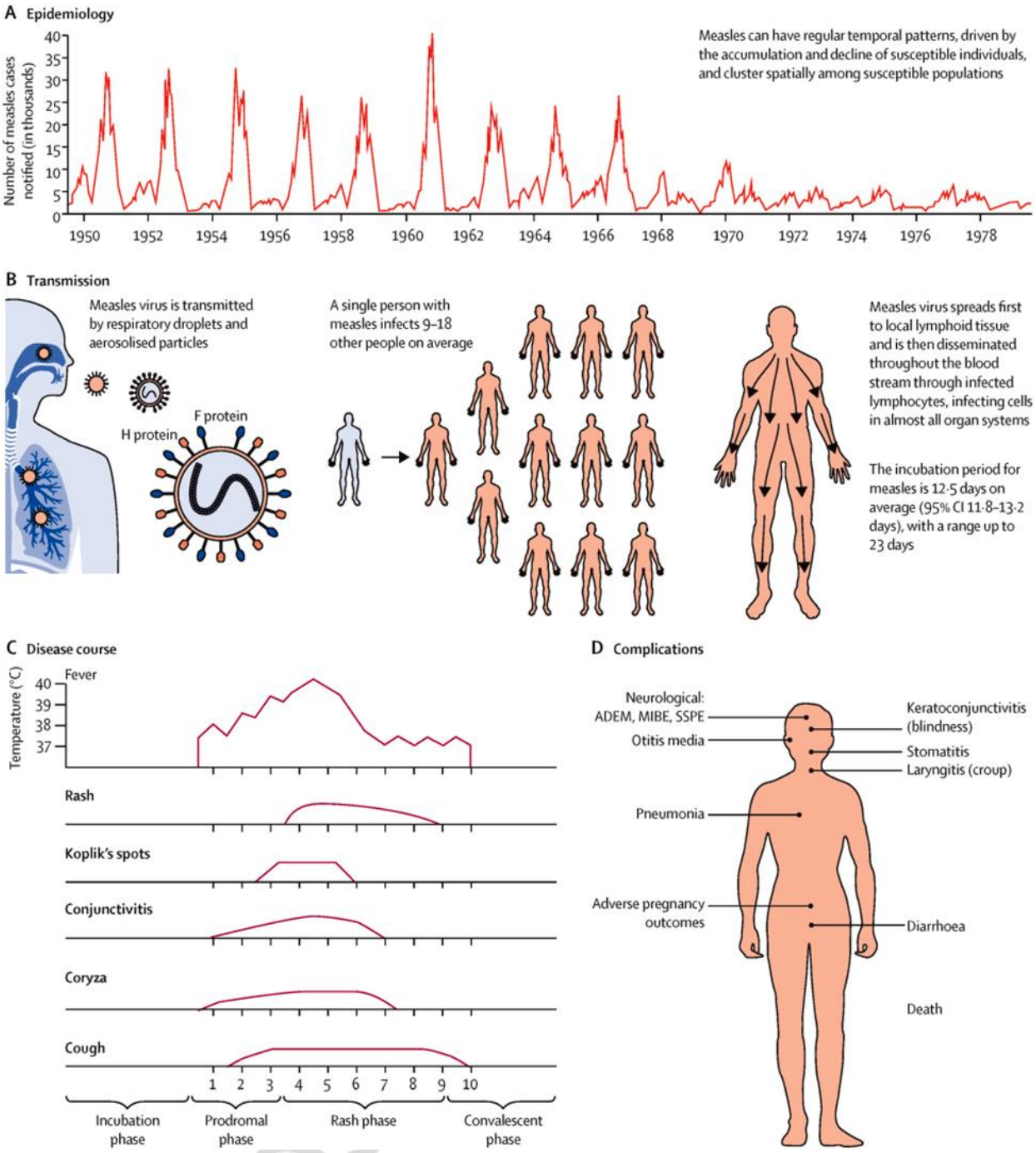

Figure 1. Measles epidemiology (A), transmission (B), disease course (C) and complications (D)

There is a short first viraemia from the pharynx to local lymph nodes, with a main second viraemia around a week after infection, leading to the dissemination throughout the blood stream through infected lymphocytes, infecting cells in almost all organ systems. It accompanied by the appearance of respiratory and intoxication syndroms, then a rash.

Infected dendritic cells and lymphocytes transfer measles virus to epithelial cells of the respiratory tract using the nectin-4 receptor. Measles virus buds from the apical surface of respiratory epithelial cells or is shed through damaged epithelium, providing respiratory transmission to susceptible hosts.

Immunity after natural infection is usually lifelong, due to both neutralizing antibody to the H protein and cell-mediated immunity.

The earliest, innate immune responses occur during the prodromal phase before the onset of rash. Two non-structural viral proteins (V and C) suppress host interferon production, facilitating virus replication. The adaptive immune response follows and consists of cellular and humoral responses, which are essential for recovery and the establishment of long-term, protective immunity, respectively.

The initial humoral response consists of IgM antibodies that arise at the time of the rash and persist for 6–8 weeks.

Subsequently, IgG antibodies are produced, the most abundant of which are against the nucleoprotein. The efficacy of antibodies alone in preventing measles is shown by the protection conferred by passively acquired maternal antibodies and post-exposure administration of antimeasles virus immune globulin.

Cellular immune responses to measles virus are important for viral clearance and recovery, as shown by the fact that children with agammaglobulinaemia recover from measles, but children with T-cell deficiencies develop severe or fatal disease.

Plasma interferon-γ levels, consistent with a predominant Th1 immune response, are increased during the acute phase of infection.

During convalescence, a Th2 response promotes the development of protective measles virus-specific antibodies and is characterised by high concentrations of interleukin 4, interleukin 10, and interleukin 13.

Measles was the first immunosuppressive infection to be described. Transient lymphopenia occurs in the blood during measles but is likely due to the redistribution of lymphocytes from peripheral blood to lymphatic tissues. Functional abnormalities of immune cells have been described, including decreased lymphocyte proliferative responses and impaired dendritic cell function ex vivo, but it is not clear that these mechanisms are responsible for immune suppression in vivo.

Measles is associated with deficiencies of both innate and adaptive immune responses leading to a transient but profound immune suppression. The clinical importance of it is illustrated by the observation that measles mortality is typically caused by secondary infection of the respiratory and digestive tracts.

Persistence of measles virus RNA for 2–3 months after rash onset could contribute to the life-long immunity and prolonged state of immune suppression following measles. Immune suppression and the associated increased risk of secondary infections are thought to last several weeks to months following measles. However, a recent intriguing study suggested this state of increased risk could extend for as long as 2–3 years after measles.

Although the infectious period for measles extends from several days before to several days after start of the rash, measles virus RNA can be detected in clinical samples for at least 3 months after rash onset.

CLINICAL FEATURES

Measles is an acute febrile illness associated with a characteristic enanthema and exanthema.

Classic measles virus infection can be subdivided into the following clinical stages: incubation, prodrome, exanthem, and recovery. Infected individuals are characteristically asymptomatic during the incubation period.

The prodromal period begins with a four-day fever (the ***4 D's***) and the ***3 C's*** – cough, coryza and conjunctivitis. The severity of conjunctivitis is variable and may also be accompanied by lacrimation or photophobia.

Filatov-Koplik spots — small 1 mm whitish, grayish or bluish spots with an erythematous base on the buccal mucosa opposite the molar teeth, though they can spread to cover the buccal and labial mucosa (figure 2). They are present about 1–3 days before the onset of the rash and provide an opportunity to clinically diagnose measles a day or two before the rash. Filatov-Koplik spots are characteristic of measles, though not found in all cases. These enanthema was described initially by Russian scientists N. F. Filatov (1885) and A. P. Belsky (1890), then in 1896 — by American pediatrician Henry Koplik.

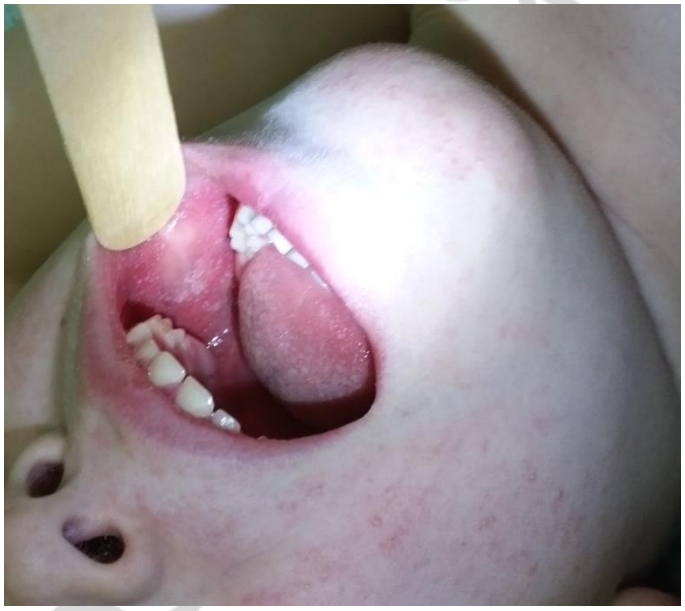

Figure 2. Filatov-Koplik spots in patient with measles on the 4th day of the disease

The prodromal symptoms typically intensify a few days before the exanthem appears.

Exanthem — maculopapular rash appears 3–4 days after the onset of fever, first behind the ears, then spreads to the trunk and extremities. Generally, the more rash, the more unwell the child is. The rash can look almost haemorrhagic. The palms and soles are rarely involved. The cranial to caudal progression of the rash is characteristic of measles but is not pathognomonic. After three to four days, the rash darkens to a brownish color (in patients of Caucasian descent though not patients of African descent) and begins to fade, followed by fine desquamation in the

more severely involved areas (figure 3). The rash usually lasts six to seven days and fades in the order it appeared.

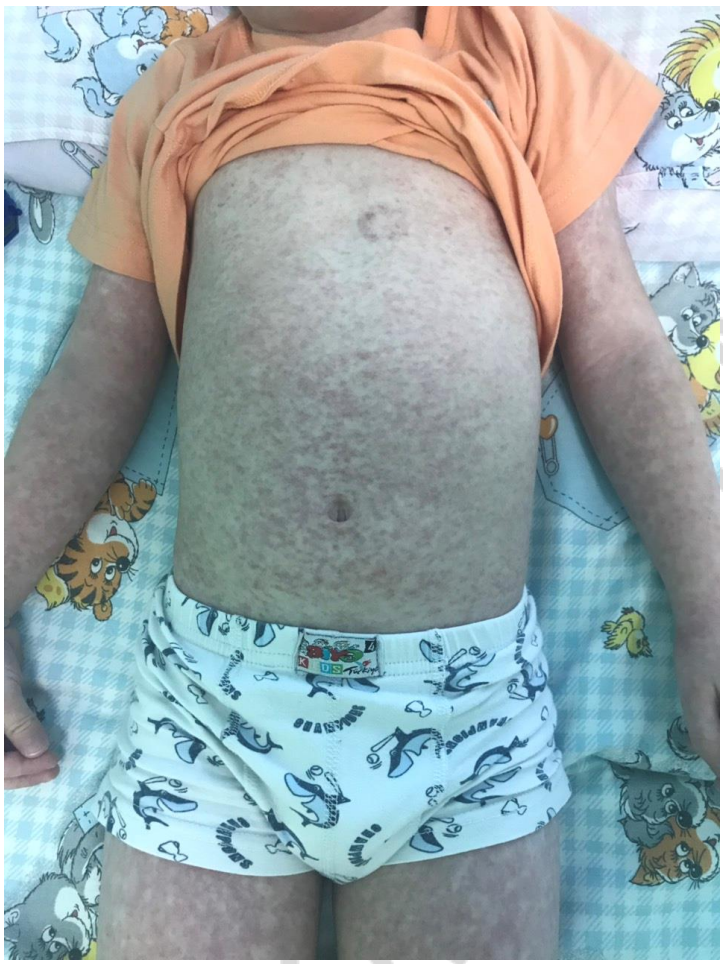

Figure 3. Maculopapular rash in patient with measles, day 3 of the rash period

The fever, catarrhal symptoms, lymphadenopathy typically peak with the rash, which persists for 3–4 days. The rash might be minimal in children with vaccine-modified measles who have previous immunity following vaccination, and these children might not have cough, coryza, or conjunctivitis.

Malnourished children usually develop a deeply pigmented rash that desquamates during recovery. As the rash represents a perivascular lymphocytic infiltration, children with impaired cellular immunity, such as those infected with HIV, might not develop the characteristic rash or the rash might be delayed.

Three days after the rash appears, children with uncomplicated measles improve and are usually fully recovered 7–10 days after the onset of illness. Cough may persist for one to two weeks after measles. The occurrence of fever beyond the third to fourth day of rash suggests a measles-associated complication.

COMPLICATIONS AND SEQUELAE

Mortality from measles is predominantly caused by complicating bacterial infections. The risk of complications is increased in developing countries, where the case fatality rate is 4 to 10 percent.

Complications occur in 6–7 % of otherwise healthy individuals in developed countries.

Complications of measles can affect different organ systems and are most common in neonates, adults older than 20 years, pregnant women, and those who are immunocompromised or undernourished, particularly children with vitamin A deficiency.

Main complications include:

– secondary infections;
– pneumonia;
– diarrhea;
– keratoconjunctivitis;
– CNS complications: acute measles encephalitis (AME), measles inclusion body encephalitis (MIBE), subacute sclerosing panencephalitis (SSPE).

Pneumonia is most often caused by secondary viral or bacterial pathogens but can be due to measles virus itself resulting in Hecht's giant cell pneumonia.

Bacterial and viral pathogens associated with pneumonia in children with measles are not well characterised, particularly in children vaccinated against pneumococcus and Haemophilus influenza type b. Pneumonia is the most common cause of measles-associated death in children; it occurs in approximately 6 percent of cases.

Other complications of the respiratory tract include otitis media, sinusitis, laryngotracheobronchitis (croup) and bronchitis. Otitis media occurs in 5 to 10 percent of cases and is more common in younger individuals.

Respiratory tract infections occur most frequently among patients <5 years and >20 years of age.

Diarrhea can result in considerable morbidity and mortality, and is often due to secondary infections with bacteria or protozoa. It occurs in approximately 8 percent of cases. Other gastrointestinal complications such as gingivostomatitis, gastroenteritis, hepatitis, mesenteric lymphadenitis, and appendicitis are very rare.

Keratoconjunctivitis or keratitis with corneal ulceration, another serious complication of measles, may lead to corneal scarring and permanent blindness, especially in children with vitamin A deficiency.

Three rare but serious ***CNS complications*** of measles were a major motivating factor to prevent infection through vaccination in countries where case fatality was low.

First, ***acute measles encephalitis*** (1.2/1000 with a lethality of approximately 15–20 %) occurs around 3–10 days after the onset of rash and begins with very high fever, severe headache, seizures, altered mentation and other neurological deficits. A person with measles encephalitis may become comatose, and death or brain injury may occur. Acute measles encephalitis (AME) may also occur in the absence of rash. CSF analysis shows lymphocytosis with elevated protein and normal glucose concentration – may be PCR-positive. A severe fulminant encephalitis has been reported. The clinical course and pathogenesis of AME are not well

understood. Although lymphoid cells are the principle targets for measles virus infection, measles can infect neurons, and appears to have several mechanisms for circumventing the blood brain barrier. Recent studies also indicate that CNS infection may be relatively common, with measles virus RNA detected by RT-PCR at autopsy in the brain of around 19 % of individuals that never had CNS disease. However, AME is often termed measles post-infectious encephalitis (PIE) or acute postinfectious measles encephalitis (APME) because symptoms generally start 3–10 days after the onset of rash. According to the fact that measles virus specific nucleic acids have been detected only by highly sensitive methods within the CNS of patients suffering from APME (Nakayama et al, 1995), the observed clinical signs are considered to result from a virally induced pathogenic immune response with autoimmune components (Liebert, 1997). Consequently it has been proposed that AME is an immune-mediated demyelinating syndrome — acute disseminated encephalomyelitis (ADEM). Some authors distinguish this form as a separate that presents during the recovery phase of measles, typically within two weeks of the exanthema. Recently assays that detect conformation sensitive myelin-reactive antibodies have detected increased levels in a subset of acute disseminated encephalomyelitis patients. Immune-modulators including intravenous immunoglobulin (IV Ig), corticosteroids and plasmapheresis have been used to treat AME, but with variable effect. Residual neurologic abnormalities are common among survivors, including behavior disorders, mental retardation, and epilepsy.

Second, ***measles inclusion body encephalitis*** (MIBE) is a progressive measles virus infection of the brain that results in neurological deterioration and death in individuals with impaired cellular immunity within months of the acute illness. MIBE has been described in children who are immunosuppressed following organ transplants and in HIV-infected persons.

Third, ***subacute sclerosing panencephalitis*** (SSPE) is a delayed complication of measles that occurs in about 1:10 000 to 1:100 000 cases 5–10 years after the acute illness, caused by the host response to production of mutated virions with defective assembly and budding. SSPE most often occurs in people infected with measles virus before 2 years of age and is characterised by seizures, progressive deterioration of cognitive and motor function, and death.

Diagnosis is based on classic EEG pattern of bilateral, high-amplitude, periodic complexes and monoclonal measles antibody titres in the CSF. The serum anti-measles antibody concentration is also elevated.

A recent report of SSPE in the USA identified a much higher incidence than previously described, including an incidence of 1:1367 cases in children who acquired measles younger than 5 years of age and 1:609 cases in children with measles before 1 year of age. Measles vaccination reduces the incidence of SSPE.

Idiopathic thrombocytopenic purpura may occur in 1 of 2, 000–3, 000 cases.

Cardiac complications of measles are rare and include myocarditis, pericarditis.

Measles in pregnancy is associated with an increased risk of low birth weight, preterm birth, spontaneous abortion, intrauterine fetal death, and maternal death. Physiologic adaptations in the immune system during pregnancy can increase a woman's susceptibility. Pregnant women infected with measles are more likely to be hospitalized, develop pneumonia, and die than non-pregnant women.

In those malnourished, especially if vitamin A-deficient, or immunocompromised, there is a higher morbidity and mortality.

There may be no rash in the immunocompromised person who present with unexplained pneumonia or encephalitis.

Mortality is greatest in infants and adults. Overall, it is about 1 in 1, 000–3, 000 in industrialized nations.

Globally, up to 5 % of deaths in the < 5 year olds are still due to measles.

DIAGNOSIS

The diagnosis of measles should be considered in a patient presenting with a febrile rash illness and clinically compatible symptoms (eg, cough, coryza, and conjunctivitis), especially in the case of recent exposure to an individual with a febrile rash illness or travel to an area of high measles prevalence, particularly in the absence of measles immunity. Patients being evaluated for measles should be isolated.

The measles case definition, consisting of a generalised maculopapular rash, fever and either cough, coryza, or conjunctivitis, has high sensitivity (75–90 %) but a low positive predictive value when measles incidence is low, highlighting the need for serological confirmation.

Laboratory diagnosis used to depend on the finding of measles-specific IgM or a 4-fold rise in IgG in blood.

Diagnosis is now possible by salivary measles-specific IgM. However, measles virus-specific IgM antibodies might be low or undetectable until 4 days or more after rash onset, resulting in false negative results if samples are collectted early. About 75 % of people with measles will have detectable measles virus-specific IgM antibodies within the first 72 h after rash and almost all people with measles will have detectable measles virus-specific IgM antibodies after 4 days.

Measles virus-specific IgM antibodies peak within 1–3 weeks after the onset of rash and decline to undetectable levels within 4–8 weeks. Anti-measles IgG is generally undetectable up to 7 days after rash onset but subsequently peaks about 14 days after the exanthem appears. The presence of IgG antibodies to measles virus in a single serum specimen is evidence of previous infection or immunisation.

Measles virus infection also can be confirmed by detection of viral RNA through real time reverse transcription polymerase chain reaction (rRT–PCR) and conventional, endpoint RT-PCR using throat, nasal, nasopharyngeal, urine samples and heparinized blood before measles virus-specific IgM antibodies are detectable. Oral fluid is the best sample – ideally collected using special kits. Viral RNA is usually present for approximately three days after rash onset.

Using RT-PCR, viral RNA allows for genotyping and epidemiological mapping.

The medical history and physical examination should focus on the clinical features of measles as well as potential complications, including pneumonia, otitis media, keratoconjunctivitis, and diarrhea. Assessment of nutritional and immune status, most importantly vitamin A deficiency and HIV infection, will identify individuals at highest risk of mortality.

The clinical diagnosis of measles is more challenging to clinicians unfamiliar with the disease, before the onset of rash, in immunocompromised and undernourished children in whom the rash might be absent or altered, and in individuals with pre-existing antibodies from maternal immunity, immune globulin, or previous vaccination who can have a longer incubation period, milder prodromal illness, and a less apparent rash than typical cases.

Laboratory findings — thrombocytopenia, leukopenia, and T cell cytopenia may be observed during measles infection. Chest radiography may demonstrate interstitial pneumonitis.

Biopsy samples of lymphoid tissues before the appearance of the exanthem may demonstrate reticuloendothelial giant cells. Histologic analysis of enanthem or exanthem and cytologic examination of nasal secretions may also demonstrate epithelial giant cells.

Histologic evaluation of conjunctival, nasopharyngeal, or buccal epithelial cells may demonstrate giant cells with inclusions; these cells may also be present in urine.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of measles depends on the clinical stage. During the prodromal period, the differential diagnosis includes common respiratory virus infections (rhinoviruses, parainfluenza, influenza, adenovirus, and respiratory syncytial virus infections).

Once an exanthem has appeared, the differential diagnosis includes rubella, enterovirus, Epstein–Barr virus infection, human herpes virus type 6 (roseola), parvovirus B19 (erythema infectiosum), dengue virus, streptococcal disease, Kawasaki disease and other conditions with rash (appendix 1).

MANAGEMENT AND TREATMENT

There is no specific antiviral therapy approved for treatment of measles.

Treatment of individual cases is symptomatic, with complications being managed individually as they arise.

The management of patients with measles consists of antipyretics (table 2), supportive therapy to correct or prevent dehydration and nutritional deficiencies, prompt recognition and treatment of secondary bacterial infections, and provision of vitamin A.

Treatment of such complications as seizures and respiratory failure may also be necessary.

Table 2

Antipyretics

Age	Dosage of antipyretics	
	Acetaminophen	**Ibuprofen**
Children over 1 months and < 12 years	10 to 15 mg/kg 3 to 4 times daily, repeated dose of 10 mg/kg should be given not earlier than in 4 hours, 15 mg/kg — in 6 hours, max. 60 mg/kg daily PO	For children over 3 months 5 to 10 mg/kg 3 to 4 times daily (max. 30 mg/kg daily) PO
Children 12 years and over and adults	500 mg to 1 g 3 to 4 times daily (max. 3–4 g daily)	200 to 400 mg 3 to 4 times daily (max. 1200 mg daily) PO

WHO recommends that all cases should be treated with vitamin A and that, even in countries where measles is not usually severe, a dose of vitamin A at diagnosis, and another a day later, should be given to all severe cases.

For children with clinical evidence of vitamin A deficiency, a third dose is recommended 2–4 weeks later.

Vitamin A for treatment of measles is administered once daily for two days at the following doses:

– Infants <6 months of age: 50, 000 international units;
– Infants 6 to 11 months of age: 100, 000 international units;
– Children ≥12 months: 200, 000 international units.

A recent Cochrane analysis reported a fall of over 60 % in pneumonia mortality associated with high-dose vitamin A use.

No specific antiviral therapy exists for measles, although ribavirin, interferon alfa, and other antiviral drugs have been used to treat severe measles.

Measles virus is susceptible to ribavirin in vitro, but data on clinical use of ribavirin are extremely limited. Some experts recommend to use ribavirin among individuals in certain risk of measles-associated mortality groups, for treatment of measles pneumonia in patients <12 months, patients ≥12 months with pneumonia requiring ventilatory support, and patients with severe immunosuppression. Ribavirin dosing consists of 15 to 20 mg/kg per day orally in two divided doses. The optimal duration of therapy is unknown. A duration of five to seven days may be reasonable, guided by the patient's clinical status (respiratory symptoms and chest radiograph findings).

Patients should be isolated until 4 days after the onset of rash.

Contacts should be traced, and consideration given to vaccination or administration of immunoglobulin, depending on their age and immunization status and the interval elapsed after contact with the index case.

PREVENTION

Measles vaccines have been available for almost 50 years. Initially, both live and killed vaccines were used. The latter caused many cases of a severe atypical infection and rapidly gave way to the live attenuated vaccines, which are the only ones now available.

The measles virus strains in commonest use are derived from the Edmonston strain (named after the boy from whom the measles virus strain was isolated). There is little to choose between them.

A single dose of a measles-containing vaccine protects 90–95 % of recipients, if given to children ≥12 months old.

The proportions of children who develop protective levels of antibody after measles vaccination are about 85 % at 9 months of age and 95 % at 12 months of age.

When measles vaccine is given to children younger than 9 months of age, a lower proportion develop protective immunity because of the inhibitory effect of maternal antibodies and immaturity of the immune system.

To attain herd immunity, it is necessary to give two doses.

WHO recommends that the first dose of measles containing vaccine be administered at 9 months of age in settings with endemic measles but as early as 6 months of age in some circumstances, including during outbreaks, for internally displaced populations and refugees, for HIV-infected and exposed children, and children at high risk of contracting measles, but allows flexibility based on local epidemiology.

High-titre vaccines were produced in an attempt to protect infants, but they are not in use due to evidence of higher non-measles death rates in recipients.

Most affluent countries give measles vaccine as part of the combined MMR vaccine. Two doses are given: one at 12–15 months, and the other at anything between 2 and 10 years later, with a few countries giving it earlier.

Side effects of the vaccine usually occur in the second week after vaccination and include a transient rash (2 %), fever and other symptoms of measles (5–10 %), febrile convulsions (1 in 3000), and idiopathic thrombocytopenia (1 in 30, 000). These reactions are much less common after the second dose.

The relative incidence of febrile seizures following MMR is higher in children vaccinated between 16 and 23 months, compared with 12 and 15 months.

Anaphylaxis after the vaccine occurs in 1 in 100, 000 or fewer recipients.

The vaccine is contraindicated in pregnancy and in individuals who are significantly immunocompromised (HIV is an exception where it may sometimes be given). Children who are infected with HIV should be revaccinated against measles following immune reconstitution with highly active antiretroviral therapy because of failure to maintain protective antibody levels.

After spurious reports of an association of MMR with autism, immunization rates fell markedly in some coutries. Following clear evidence of absolutely no link between MMR and autism, national immunization rates rose again and now exceed pre-scare levels among 2-year-old children.

It may be possible to prevent disease in susceptible contacts.

Immunosuppressed individuals, whose last contact was within 6 days, should have an urgent assessment of antibody levels and given human normal immunoglobulin (HNIG) if negative or equivocal.

If urgent testing is not possible, immunoglobulin as HNIG should be given. The dose recommended is 0.6 mL/kg subcutaneously or 0.15 g/kg IV.

Infants <1 year should be given 0.6 mL/kg IM, up to a maximum of 5 mL.

As the incubation period of the vaccine virus is shorter than that of wild measles virus (7 as opposed to 10 days), if given within 3 days of exposure, MMR or measles vaccination reduces the risk of development of measles.

A combined MMRV (measles, mumps, rubella, and varicella) vaccine is available in some countries. When the first dose is given at or below 47 months of age, there is an increased risk of fever, febrile convulsions, and rash, when compared with MMR and varicella vaccines given separately, but on the same occasion. For this reason, in the US, it is advised that, when the first dose of MMR is given at or below 47 months, it should not be given as part of MMRV.

Infection control — in the inpatient setting, airborne transmission precautions are indicated for four days after the onset of rash in otherwise healthy patients and for the duration of illness in immunocompromised patients. Susceptible individuals should not enter the room of patients with suspected or confirmed measles. Exposed susceptible individuals should be work excluded from day 5 through day 21 after exposure. If the case is confirmed, even those who were vaccinated within 72 hours should be excluded.

In the outpatient setting, patients with febrile rash illness should be escorted to a separate waiting area or placed immediately in a private room, preferably at negative pressure relative to other patient care areas. Both patients and staff should wear appropriate masks/respirators (masks for patients to prevent generation of droplets, and respirators for staff to filter airborne particles, regardless of immunity status). If not admitted, patients should be told to remain in isolation at home through four days after rash onset. Measles virus can remain suspended in the air for up to two hours; therefore, the room occupied by a suspect case should not be used for two hours after the patient's departure.

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately.

RUBELLA

Rubella, also known as «German measles» or «3-day measles» is a relatively mild disease characterized by rash, lymphadenopathy and low-grade fever. Nevertheless, this illness has serious consequences in pregnant women causing a variety of birth defects known as congenital rubella syndrome. Worldwide, an estimated 110, 000 babies are born with CRS every year.

HISTORICAL BACKGROUND

It is known that ancient physicians of the South East Asia recognized a rush that presumably was rubella. They considered it to be a variant of measles and referred to it as al-hamikah. German physicians in the early 1800th called it Roetheln. It was first described in the English literature as a separate disease by Manton in 1815, and later was called rubella, a «short and euphonious» name, by Veale in 1866. Rubella has not been the focus of a major interest because it was generally presumed as a mild, self-limited disease with few serious complications.

In 1941, Sir Norman McAlister Gregg, an Australian ophthalmologist from the Yale University School of Medicine, New Haven, Connecticut made a great discovery by describing congenital rubella syndrome. Doctor Gregg reported that an unusual number of newborns with congenital cataracts had suddenly appeared in Sydney and elsewhere in Australia, and that in almost all cases the mothers of the infants had experienced rubella in the first trimester of pregnancy. He also noted the presence of other ocular abnormalities in the affected infants as well as a high incidence of cardiac lesions.

The medical community was slow to accept his findings and an editorial published in The Lancet in 1944 questioned their validity. But once the disease had been pointed out, confirmatory reports of Gregg's remarkable discovery began to come in from various parts of the world during the next decade.

The viral nature of the infection was confirmed in 1938 by Hiro and Tasaka which produced rubella in children by inoculation nasopharyngeal secretions taken from rubella patients. In volunteer studies in 1953 Krugman and Ward showed that viremia occurs in the preeruptive stage and proved that the infection can occur without rash.

During the next decade a lot of attempts were made to cultivate rubella virus in vitro. Finally, in 1962 this was accomplished. Two different groups of investigators, Weller and Neva at the Harvard School of Public Health and Parkman, Buescher, and Artenstein at the Walter Reed Army Institute of Research, simultaneously reported the growth of rubella virus in cultured cells. This breakthrough was a landmark: it made possible an accurate delineation of the clinical epidemiology of the disease, made available tools to determine the behavior of the virus in population groups, and, most significantly, provided the basis for the development of vaccines for the control of congenital rubella. Three rubella vaccines were licensed in the United States in 1969–1970 and became widely used.

ETIOLOGY

Rubella is caused by rubella virus (RV) the sole member of the genus Rubivirus that belongs to the Togaviridae family. RV is an enveloped virus with a 9.6-kb single-stranded, positive-sense RNA genome. Rubella virus has an irregular helical organization of its surface glycoproteins and a pseudo-tetrameric inner nucleocapsid arrangement. The glycoprotein arrangement in rubella virions is unique. Currently, rubella virus is the only known example of a helical surface structure associated with

a membrane enveloped virus. The virions have particle diameters ranging from 60 to 80 nm, with most of the spherical virions having a diameter of about 70 nm. RV encodes two nonstructural (p150 and p90) and three major structural proteins: a capsid protein (~31 kDa), glycoproteins E1 (58 kDa) and E2 (42–47 kDa). The nonstructural proteins are required for viral replication and transcription. The capsid protein interacts with the RNA genome and forms the nucleocapsid, which is surrounded by a lipid membrane upon which E1 and E2 are arranged. Proteins E1-E2 form the glycoprotein spikes on the virion surfaces and are responsible for receptor binding and membrane fusion during virus entry. The glycoprotein E1 brings about receptor-mediated endocytosis and is the immunodominant antigen. The glycoprotein E2 is membrane bound and forms connections between rows of E1 glycoproteins. The capsid protein in addition to its structural roles in nucleocapsid formation and virus budding, modulates replication of viral RNA and alters mitochondrial physiology by exerting antiapoptotic effect via multiple mechanisms, which include interactions with host cell proteins or lipids.

Although RV has one serotype, sequence analyses of the E1 glycoprotein showed that distinct genetic variants of rubella virus exist. RV is classified into two clades. Clade 1 is divided in 10 genotypes (1a, 1B, 1C, 1D, 1E, 1F, 1G, 1H, 1I, and 1J) of which nine are recognized (uppercase letter) and one is provisional (lowercase letter). Clade 2 is divided in three genotypes (2A, 2B, and 2C).

RV can be grown in many primary and continuous cell lines derived from human, non-human primate, and other vertebrate tissue. Induction of apoptosis appears to be the primary mechanism by which cytopathic effect is produced.

EPIDEMIOLOGY

Rubella occurs worldwide with a seasonal distribution. Humans are the only known host. The mechanism of transmission in acquired rubella is mostly droplet. RV is transmitted by the respiratory route, rarely by contact in daily life. The source of infection are infected individuals with manifest or asymptomatic disease. The risk of infection is augmented by close and prolonged contact with infected individuals. In many cases, rubella infection is asymptomatic, and the shedding and infectiousness of the infected individual is never recognized.

Congenital infection occurs when maternal viremia allows hematogenous spread of the virus across the placenta. The highest risk of maternal-fetal transmission occurs in the first trimester and after 36 weeks gestation. However, the risk of congenital defects after maternal infection is essentially limited to maternal infection in the first 16 weeks of pregnancy.

RV can be found in nasopharyngeal samples from 7–13 days before the onset of the rash to 2–3 weeks after, with maximal shedding occurring 1–5 days after the rash onset. Infants with congenital rubella may excrete the virus for a year or more in pharyngeal secretions and urine.

Rubella is highly communicable disease with index of contagiousness about 75–90 %, up to 100 % in household contacts.

RV is unstable in the environment and readily inactivated by chemical agents such as chlorine, deoxycholate, formalin, ultraviolet light, but it is resistant to antibiotics.

In the absence of vaccination, the mean age of rubella infection is 5–9 years, with annual seasonal outbreaks usually occurring in the winter and spring and large epidemics every 3–8 years. The seasonal pattern is most marked in the West and the South Africa, with the Central and the East Africa having a bimodal pattern with transmission throughout the year. The cyclical nature of rubella is related to the build-up of susceptible people in the population and contact rates.

Immunity. The previous disease or vaccination leads to the formation of lifelong immunity Reinfection is uncommon and usually is subclinical. Nevertheless, in some cases reinfection is possible. Re-exposure can produce a significant rise in the pre-existing titer of IgG antibodies, but rarely results in detectable viremia or risk to a developing fetus. A few cases of fetal infection following maternal reinfection have been reported, however.

The effectiveness of rubella vaccination is well known and the ≥10 IU/mL antibody level is protective in the vast majority of persons.

Contemporary epidemic features. Rubella occurred worldwide in prevaccination period. The largest rubella epidemic that occurred in the United States during 1964–1965 resulted in an estimated 12,5 million cases of rubella, including >2000 cases of encephalitis, > 11, 250 cases of fetal wastage, > 20, 000 cases of CRS, >8 000 cases of deafness, 3 580 deaf–blind children and 1 800 children with mental retardation.

Thanks to active vaccination in the world, started in the USA in 1969–70 and later adopted by other countries, the incidence of rubella has dramatically declined. During 2000–2012, rubella cases reported worldwide decreased by 86 % from 670, 894 to 94, 030 among the WHO member states. In 2015, rubella was officially declared eliminated from the Americas.

Despite tremendous progress made towards rubella elimination in the latest decades rubella outbreaks continue to occur in other parts of the world, and CRS remains a concern. The recent rubella outbreak in Japan (2012–13) counted 15, 000 cases of rubella and 43 cases of congenital rubella syndrome, with more than 80 % of rubella cases reported in Tokyo and Osaka. This resurgence of rubella has mainly affected adult men aged 35–51 years – who had not received routine rubella vaccine during their childhood when only schoolgirls were vaccinated, and men and women aged 24–34 years – whose vaccine coverage rates were relatively low. Thus, the hallmarks of the national vaccination schedule and the persistence of susceptible persons in the population can have a strong impact on the epidemic development.

Number of reported rubella cases in WHO regions during 2017 and 2018 was 16, 283 and 10, 976 respectively. The recent major outbreaks of rubella with incidence more than 100 cases per year were detected in 18 countries worldwide (appendix 2).

PATHOGENESIS

Acquired rubella. After inhalation of infectious aerosols initial replication occurs in nasopharyngeal cells and regional lymph nodes. Viremia occurs five to seven days after inoculation, allowing the virus to spread throughout the body. The virus can be isolated from the pharynx and blood during this period and on occasion may be isolated subsequently from a number of other sites including synovial fluid, urine, bronchoalveolar lavage fluid, and cerebrospinal fluid.

Infected individuals may shed virus and are potentially contagious for one to two weeks before the infection becomes clinically apparent. With the appearance of the rash, typically 14 to 17 days after exposure, viral shedding decreases concurrent with the development of neutralizing antibodies. Therefore, the rash has been postulated as being immune-mediated.

Congenital Rubella. The pathogenesis of rubella virus infection in fetuses remains unclear. It is considered that the RV infects the epithelium of the chorionic villi and the capillary endothelium of the placenta causing chronic ischemia of the fetus tissues and organs. The RV reaches to the fetus through the bloodstream in the form of the smallest emboli which inhibiting cell growth. The virus causes disturbances in the mitotic activity of the cells and chromosomal changes leading to the fetus death or development of the severe birth defects.

The recent study based on the pathological examination of aborted fetuses with CRS demonstrated that the rubella virus infection occurred via systemic organs of human fetuses including circulating hematopoietic stem cells. Viral RNA was detectable in all of the major organs such as the liver, kidney, spleen, heart, lungs, the eyes and CNS (consisting of the cerebral cortex, cerebellum and brain stem.

The risk of birth defects declines with infection later in gestation and fetal defects are rarely associated with maternal rubella after the 16th week of pregnancy, although sensorineural hearing deficit can occur with infection as late as week 20. Infection in the late stages of pregnancy leads to the development of systemic inflammation. CRI is progressive chronic persistent disease.

CLASSIFICATION OF RUBELLA

Rubella virus infection leads to acquired or congenital disease.

The following clinical forms of acquired rubella are distinguished:

1) typical;
2) atypical, which are presented by next forms:

– inapparent;
– subclinical;
– with isolated rash;
– with isolated lymphadenopathy.

Classification of rubella in International Classification System of Diseases for Mortality and Morbidity Statistics includes:

B06.0 Rubella with neurological complications

B06.9 Rubella without complication
P35.0 Congenital rubella syndrome
B06.8 Rubella with other specified complication.

CLINICAL FEATURES

Acquired rubella infection. The typical form of acquired rubella is characterized by the presence of following syndromes: exanthema, lymphadenopathy and catarrhal.

Depending on the severity of intoxication syndrome and local signs, mild, moderate and severe rubella can be distinguished. The disease is mild in most cases. The body temperature is normal, less often is subfebrile, the child's well-being is not disturbed, there are no symptoms of intoxication. Moderate and severe forms of rubella are characterized by febrile temperature and severe intoxication syndrome, though are rarely observed, mainly in older children, adolescents and adults.

The incubation period of rubella is usually 11 to 23 days (ranges 10 to 25 days).

The prodromal period lasts from several hours to several days (up to 5), in young children is more often absents. Mild ***catarrhal signs*** usually occur at the beginning of the disease: coryza, nonexudative conjunctivitis, throat irritation, infrequent dry cough, mild hyperemia of the palatine arches and posterior pharyngeal wall, and petechiae on the soft and hard palate is called ***Forchheimer spots*** (figure 4). Primary infection among adolescents and adults tends to be of longer duration than that among young children. Patients are more frequently symptomatic, and symptoms are more frequently accompanied by a prodrome of fever and systemic complaints such as malaise, fatigue, headache, eye pain and arthralgia.

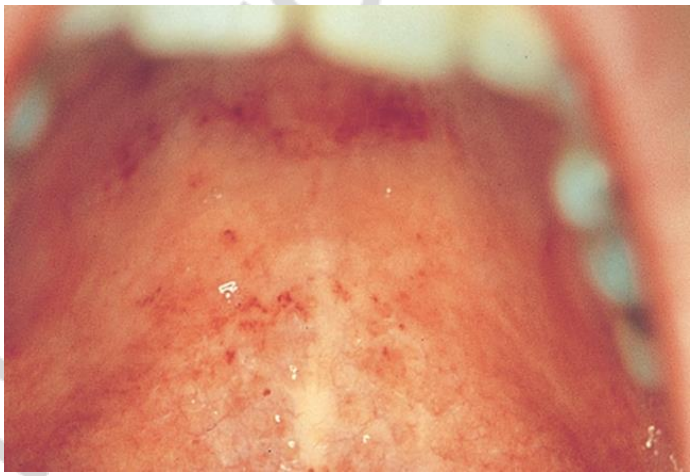

Figure 4. Petechiae on the hard palate of the same individual (Forchheimer spots)

Lymphadenopathy may occur concurrently or one to five days prior to the appearance of the exanthem. The lymphadenopathy characteristically involves the posterior cervical, posterior auricular, and suboccipital lymph nodes. Generalized involvement may be observed manifesting increased axillary and inguinal lymph nodes. The adenopathy is usually moderate but can be multiple or isolated in the

form of asymmetrical damage of one lymph node. Lymph nodes are elastic in consistency, slightly tender, usually enlarge up to 1–2 cm in diameter.

A rubella rash appears simultaneously on the first, less often on the second day of the disease. The first elements of the rash appear on the face, they quickly spread within 1–1.5 days on the neck, trunk, limbs. The eruptions in most patients are pale pink, finely spotted, rather abundant. The elements of rash are disposed on the unchanged skin background and are almost monomorphic with even edges. The predominant rash localization is extensor surfaces, but it can also be quite abundant in the flexion regions. In some cases, the rash may be bright, large maculopapular, with a tendency to merge.

The rubella rash is bright, large, especially on the face on the first day. Next day the rash may change to fine-spotted, scarlet-like and located both on the flexor surfaces and extensor. On the third day the rash fades, becomes less abundant, and localizes mainly on the extensor surfaces of the shoulders, forearms, buttocks and on the outer part of the thighs. The rash is usually not observed on the palms and soles.

The rash disappears without a trace, usually by the fourth day of the disease. In rare cases pigmentation remains for 2–3 days.

The atypical forms of acquired rubella. Acquired rubella infection is asymptomatic or subclinical in more than fifty per cent of cases. The inapparent form of rubella is characterized by asymptomatic course and development of immune response in the form of the appearance of specific antibodies. The subclinical form is appeared by ephemeral rash, the lightest and poorly expressed clinical manifestations. There are increased lymph nodes, short-term subfebrile temperature, and hematological changes. In some cases there is only isolated rash or isolated lymphadenopathy. Atypical forms are difficult to recognize since their diagnosis is impossible to make only on the basis of clinical findings.

Acquired rubella usually proceeds without any complications. However, it may have an unfavorable effect on the course of other diseases.

Congenital rubella infection (CRI) encompasses all outcomes associated with intrauterine rubella infection (eg, miscarriage, stillbirth, combinations of birth defects, fetal growth restriction or asymptomatic infection).

Congenital rubella syndrome (CRS) — refers to variable constellations of birth defects (eg, hearing impairment, congenital heart defects, cataracts/congenital glaucoma, pigmentary retinopathy, etc).

CRI is rare in developed countries with established rubella national immunization programs. However, CRS rates are highest in the WHO African and South-East Asian regions where vaccine coverage is the lowest.

CRI involves multiple organ systems and has a long period of active infection and virus shedding in the postnatal period. The risk of maternal-fetal transmission and clinical manifestations of CRI depending upon the time of maternal infection. The highest risk of transmission is in the first 10 weeks of gestation. Structural cardiac and eye defects typically result when maternal infection occurs

before eight weeks. Congenital defects are unlikely if maternal infection occurs after 18 to 20 weeks gestation. Early in the third trimester, however, the rate of infection increases again and finally reaches a high level.

Deafness, cataracts, and heart defects, which are called ***Gregg triad***, are the classic manifestations of CRS.

Cataracts occur in approximately one-quarter of infants with CRS; infantile glaucoma is less frequent (figure 5). Cataracts and infantile glaucoma usually become apparent during the early weeks of life.

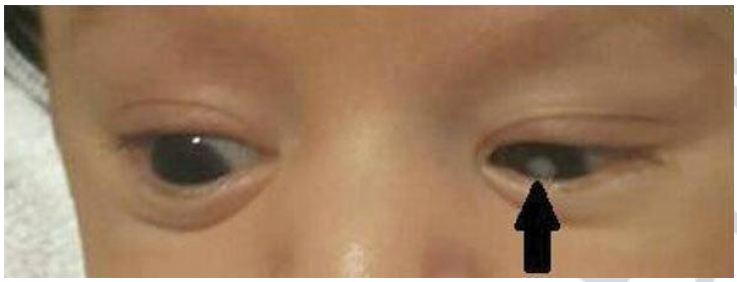

Figure 5. Cataract (arrow) in case-patient with CRS. Patient was 4 weeks of age

The following ***cardiac defects*** have been documented the most frequently: pulmonary artery stenosis, patent ductus arteriosus, septal defects. Less often aortic stenosis, tetralogy of Fallot, aortic coarctation, transposition of the great vessels, Ebstein's anomaly, and pulmonary artery coarctation have been reported.

Brain abnormalities such as microcephaly, hydrocephalus, cerebral calcifications, anencephaly, cerebellar vermis agenesis, corpus callosum hypoplasia, and hydranencephaly can be observed.

Genitourinary disorders in CRI include: vesicoureteral reflux, renal agenesia, hydronephrosis, hypospadias, ectopic testicles, inguinal hernias, and hydrocele.

There are a lot of varied clinical manifestations of CRI have been observed during the neonatal period: fetal growth restriction, meningoencephalitis, interstitial pneumonia, petechiae and purpura, representing so-called blueberry muffin lesions, hemolytic anemia, thrombocytopenia, generalized lymphadenopathy, hepatosplenomegaly, jaundice, hepatitis, diarrhea, radiolucent bone lesions in metaphyses.

The majority of infants with CRI are asymptomatic at birth but develop manifestations over time. Some of the late manifestations may relate to subtle damage that is present but not detected in early life. Late-onset manifestations include: hearing loss, eye problems, immune defects, endocrine disorders, vascular effects, and progressive panencephalitis.

Permanent hearing loss is the most common late manifestation of CRI, ultimately occurring in up to 80 % of patients. Hearing loss is usually sensorineural and bilateral. It ranges in severity from mild to profound and may progress over time. Rarely, sudden onset of hearing loss may occur after years of normal hearing.

Eye problems due to CRI are characterized by development of pigmentary retinopathy, cataracts, glaucoma, keratic precipitates, keratoconus, corneal hydrops, microphthalmos, strabismus, and absorption of the cataractous lens. This damage can appear years or even decades after birth.

Defects in specific antibody production, repeated infections, and defective T-cell response with associated autoimmune phenomena have been observed in patients with CRS.

Endocrine disorders include diabetes mellitus type 1, thyroid disease, and growth hormone deficiency.

Vascular sequelae of CRS may include fibromuscular proliferation of the intima, sclerosis of arteries, systemic hypertension secondary to renal disease, and subretinal neovascularization. These lesions are potential causes of coronary, cerebral, and peripheral vascular disease in adulthood.

Progressive rubella panencephalitis **(PRP)** most commonly occurs in the second decade of life. It is slowly progressive and fatal. The disease usually starts from learning problems and coordination dysfunction. The main neurological features of PRP are dementia, cerebellar ataxia, and seizures. Increases in antirubella antibody titer and IgG are found in the CSF and diffuse atrophy of the brain with ventricular dilatation may be found on magnetic resonance imaging. The pathomechanism of PRP remains unclarified.

The individual defects noted in congenital rubella syndrome are not specific only for CRS and may occur in other fetal infections.

COMPLICATIONS

Complications of rubella are infrequent. ***Arthritis*** and arthralgias are the most common noted among teenagers and adults rather than children. They usually occur concurrently with the rash and may persist for a month or more. The knees, wrists, and fingers are the most frequently involved. Although cases of chronic arthritis with rubella have been reported occasionally, the role of rubella virus in causing chronic forms of arthritis is uncertain.

Postinfectious encephalitis is one of the most serious complications of rubella, but it is extremely rare**.** According to the different authors, frequency of encephalitis varies from 1: 4, 000 to 1: 13, 000 cases of rubella, usually within a week of the exanthema, but may occur without any rash. Clinical manifestations of encephalitis are accompanied by headache, vomiting, and a new temperature rise up to febrile level. Severe cerebral symptoms appear, various degrees of consciousness disorder from lethargy to deep coma increasing during a short period from several hours to 1–2 days. Almost all patients develop tonic-clonic seizures. Hallucinations and delirium are possible. The polymorphic focal neurologic deficits join quickly. Reverse development of focal neurologic signs lasts about 2–3 weeks, but in some cases it can be delayed up to 1–1.5 months. In general, the prognosis is good, although fatal cases have been reported.

Thrombocytopenia, which appears more common in children than in adults, is usually self-limiting but can last days to months.

Other rare complications include myocarditis, pericarditis, Guillain-Barré syndrome, hemolytic anemia, hepatitis, and orchitis.

DIAGNOSIS

WHO established the definitions for rubella. The clinical criteria for rubella is maculopapular rash and cervical, suboccipital or post-auricular adenopathy, or arthralgia/arthritis. The laboratory criteria for rubella is rubella IgM antibody detection or rubella virus isolation or rubella viral RNA detection by PCR or a significant rise in rubella IgG antibody in paired sera.

Investigation of blood should be carried out from 4^{th} to 7^{th} day from the rash onset to identify specific antibodies in acquired rubella. EIA is used for detection of rubella antibodies. Recent infection may also be detected by measurement of low avidity IgG rubella antibodies.

To detect the virus genome a nasopharyngeal swab, urine, and blood are examined. The samples should be taken in the first 2 days but not later than 7 days from the rash onset.

Leukopenia, lymphocytosis, and normal level of ESR are revealed in acquired rubella in blood test.

The clinical criteria of CRS include sensorineural hearing loss, and (or) congenital heart disease, and (or) pigmentary retinopathy, and (or) cataracts, and (or) congenital glaucoma and one or more symptoms such as purpura, splenomegaly, microcephaly, growth retardation, meningoencephalitis, radiographic bone lucencies, jaundice, which developed within 24 hours after birth, in child aged less than 1 year.

The laboratory criteria confirming CRS in children under 1 year of age is accomplished by the detection of IgM antibodies to rubella virus in serum blood or stable level of IgG antibodies in their examination twice at least at age from 6 to 12 months (with no rubella vaccination), detection of rubella virus (including viral nucleic acid detection or virus isolation) in clinical specimen.

DIFFERENTIAL DIAGNOSIS OF RUBELLA

Acquired rubella should be differentiated from other diseases which are accompanied a rash, primary from viral and bacterial infections, as well as allergic and autoimmune reactions (appendix 1).

Many rash illnesses may mimic rubella infection, but at the same time many rubella infections remain unrecognized. A recent study was conducted to determine the incidence of measles virus, rubella virus, human parvovirus B19, enterovirus, adenovirus, and human herpesvirus 6 in measles or rubella suspected patients in Belarus. A total of 856 sera sent to the WHO National Laboratory were tested for specific IgM antibodies to measles virus, rubella virus and human parvovirus B19. The negatives were further investigated for antibodies to enterovirus and adenovirus. Children of up to 3 years were tested for IgM antibodies to human herpesvirus 6. A viral etiology was identified in 451 (52.7 %) cases, with 6.1 % of the samples being positive for measles virus; 2.6 % for rubella virus; 26.2 % for human parvovirus B19; 9.7 % for enterovirus; 4.6 % for adenovirus; and 3.6 % for human herpesvirus 6.

Measles, when compared to rubella, is characterized by more marked catarrhal signs and more severe intoxication syndrome. The appearance of Filatov-Koplik spots on the mucous membrane, staging of eruptions and pigmentation are pathognomonic symptoms of measles.

Severe throat pain, tonsillitis with distinct hyperemia, and purulent exudates, regional lymphadenitis; red finely punctate rash, specific dynamics of the tongue purification from white to strawberry are typical for scarlet fever. Respiratory symptoms and conjunctivitis are usually absent in contrast to rubella.

Enterovirus infection is characterized by polymorphism of clinical manifestations including an acute onset of disease, febrile fever and significant intoxication syndrome. The rash appears later than in rubella. The appearance of vesicular pharyngitis indicates the enterovirus nature and never occurs in rubella.

Exanthema associated with parvovirus B19 infection especially in patients with arthralgia and arthritis may be suspicious for rubella. The rash does not appear immediately but usually in 3–6 days after the onset of mild flu-like symptoms. Erythematous rash develops on both cheeks, nasolabial folds, as well as circumoral and periorbital regions, giving the appearance that the cheeks have been slapped. Then erythematous skin eruptions subsequently develop on the trunk, spreading to the arms and legs. The skin lesions are often itchy. Thereafter, rash gradually clears from the center outwards, giving a characteristic reticular or 'lacy' morphology which is a pathognomonic sign of this infection. The rash can then wax and wane for ~3 weeks, reappearing because of different factors, such as exposure to sunlight and an increase in temperature. The rubella rash disappears with a few days without a trace and no recurs.

Allergic rash in most cases is maculopapular, with urticarial elements, which are various shape and size, and are accompanied by itching.

MANAGEMENT AND TREATMENT

Patients are recommended a plenty of fluid and a bed rest in the acute period of the disease. No specific therapy for rubella infection is available. Management is supportive and symptomatic. Antipyretics such as acetaminophen and ibuprofen should be used in children with axillary temperature ≥38.5 °C (table 2). Patients with rubella arthritis are indicated to administer non-steroidal anti-inflammatory drugs for 5 to 7 days. In cases of skin itch may be used antihistamines, but usually are not necessarily.

In most cases, the patients with acquired rubella can be treated in outpatient departments. Children with complications and/ or severe clinical manifestations must be hospitalized. Hospitalization is also indicated for children from enclosed settings, persons living in dormitories or in dysfunctional families. Discharge patients with rubella from a hospital are carried out after clinical recovery but not earlier than 7 days from rash onset.

PREVENTION

Under the Global Vaccine Action Plan, measles and rubella are targeted for elimination in five WHO Regions by 2020. The plan includes a five-pronged strategy:

1) to achieve and maintain high levels of population immunity by achieving ≥95 % vaccination coverage with two doses of measles- and rubella-containing vaccines;

2) to monitor disease using effective surveillance, and to evaluate programmatic efforts;

3) to develop outbreak preparedness and to respond rapidly to outbreaks;

4) to communicate and engage to build public awareness and confidence in immunization;

5) to perform the research and development needed to support cost-effective operations and to improve vaccination and diagnostic tools.

The specific prevention of rubella is vaccination. Rubella vaccine was introduced nationwide in 162 (from 194) countries by the end of 2017, and global coverage was estimated at 52 %. The rubella vaccine is a live attenuated strain, and a single dose gives more than 95 % long-lasting immunity, which is similar to that induced by natural infection.

Rubella vaccines are available either in monovalent formulation (vaccine directed at only one pathogen) or more commonly in combinations with other vaccines such as with vaccines against measles (MR), measles and mumps (MMR), or measles, mumps and varicella (MMRV). In most countries are recommended children get two doses of MMR vaccine, starting with the first dose at 12 through 15 months of age, and the second dose at 4 through 6 years of age.

Adverse reactions following vaccination are generally mild. They may include pain and redness at the injection site, low-grade fever, rash and muscle aches.

The nonspecific prevention of rubella includes isolation of patient up to 7 days from the rash onset.

During the first 72 hours after contact of the index patient at the site of infection ***emergency immunization*** of contact persons is needed to prevent the spread of rubella. To avoid CRS women of childbearing age should have their immunity checked and receive rubella vaccine if needed.

STREPTOCOCCAL INFECTION

HISTORICAL BACKGROUND

Streptococci were demonstrated in cases of erysipelas and wound infections by Billroth in 1874 and in the blood of a patient with puerperal sepsis by Pasteur in 1879. Fehleisen, in 1883, isolated chain forming organisms in pure culture from erysipelas lesions and then demonstrated that these organisms could induce typical erysipelas in humans. Rosenbach applied the designation Streptococcus pyogenes to these organisms in 1884.

CLASSIFICATION OF STREPTOCOCCI

Streptococci are Gram-positive cocci, which are responsible for a wide variety of clinical diseases. They divided into 3 groups (alpha-, beta- and gamma-hemolytic streptococci) based on their specific hemolytic ability. ***Beta-hemolytic streptococci*** completely lyse the red blood cells, leaving a clear zone of hemolysis around the colony. ***Alpha-hemolytic streptococci*** only partially lyse the RBCs, leaving a greenish discoloration of the culture medium surrounding the colony. ***Gamma-hemolytic streptococci*** are unable to hemolyze the RBCs.

The streptococci can also be classified based on the antigenic characteristics of the C carbohydrate on the cell wall. These antigens are called Landcefield antigens and are given letter names (from A, B, C, D, E, through S).

According to Lancefield group-specific antigen the following medically important groups are (*table 3*):

– Group A: Streptococcus pyogenes;
– Group B: Streptococcus agalactiae;
– Groups C and G: Streptococcus dysgalactiae and Streptococcus equisimilis;
– Streptococcus pneumonia.

Table 3

Classification of Streptococci

Lancefield's group	Representative species	Hemolytic pattern	Typical infections
A	**S. pyogenes**	β	Pharyngitis, pyoderma / impetigo, erysipelas, cellulitis, scarlet fever
B	**S. agalactiae**	β	Neonatal sepsis and meningitis, puerperal infection, urinary tract infection, endocarditis
C, G	S. dysagalactiae S. equisimilis	β	Cellulitis, endocarditis
D	Enterococci: **E. faecalis, E. faecium**	Usually nonhemolytic	Urinary tract infection, endocarditis
Variable or nongroupable	**S. pneumoniae**, S. bovis, S. sanguis, S. mitis, S. intermedius, S. anginosus, S. constellatus, Peptostreptococcus magnus	α Usually nonhemolytic	Pneumonia, meningitis, Otitis media and sinusitis, dental abscess, brain abscess

ETIOLOGY

Beta-hemolytic streptococci group A (Streptococcus pyogenes) — is one of the leading pathogenic bacteria that infects children and adolescents, and is associated with a wide spectrum of infections and disease states. Worldwide, there are estimated to be > 600 million cases of GAS pharyngitis («strep throat») and > 100 million cases of GAS pyoderma annually.

The vast majority of GAS infections are of short duration and are relatively benign; however, invasive disease can be fulminant and life threatening.

GAS can cause a diverse variety of suppurative diseases and nonsuppurative postinfectious sequelae.

The *suppurative* spectrum of GAS diseases includes the following:

– pharyngitis — with or without tonsillopharyngeal abscess;
– impetigo — purulent, honey-colored, crusted skin lesions;
– necrotizing fasciitis;
– cellulitis;
– streptococcal bacteremia;
– osteomyelitis;
– otitis media;
– sinusitis;
– meningitis or brain abscess (a rare complication resulting from direct extension of an ear or sinus infection or from hematogenous spread).

The *nonsuppurative* sequelae of GAS infections include the following:

– acute rheumatic fever;
– rheumatic heart disease — Chronic valvular damage, predominantly the mitral valve;
– acute glomerulonephritis.

GAS is a gram-positive coccoid-shaped bacterium that grows in chains. GAS produces small white to grey colonies with a clear zone of β-hemolysis on blood agar.

***The major virulence factors for Streptococcus pyogenes are*:**

– *M-protein* (80 types) — inhibits the activation of complement and protects the microorganism from phagocytosis;

– *Streptolysin O* — destroys red and white blood cells. Streptolysin O is produced by almost all strains of S. pyogenes (as well as many group C and G organisms) and is antigenic. Measurement of antistreptolysin O antibodies in human sera has proved exceedingly useful as an indicator of recent streptococcal infection;

– *Pyrogenic exotoxins (erythrogenic toxins)* are found in only a few strains. They are a family of bacterial superantigens believed to be associated with streptococcal toxic shock syndrome, necrotizing fasciitis, and other severe infections. This family includes the bacteriophage-encoded SpeA50 and SpeC, historically known as the scarlatinal toxins because of their association with scarlet fever, as well as the cysteine protease SpeB.

Several extracellular products may theoretically serve to facilitate the liquefaction of pus and the spreading of streptococci through tissue planes characteristic of streptococcal cellulitis and necrotizing fasciitis. These include the following:

1. Four antigenically distinct enzymes that participate in the degradation of deoxyribonucleic acid (DNases A, B, C, and D);

2. Hyaluronidase, which enzymatically degrades hyaluronic acid found in the ground substance of connective tissue;

3. Streptokinase, which promotes the dissolution of clots by catalyzing the conversion of plasminogen to plasmin;

4. Streptococcal pyrogenic exotoxin B (SpeB), which is a potent protease;

5. C5a peptidase, which specifically cleaves the human chemotaxin C5a at the PML binding site. SpeB also cleaves IgG bound to GAS, thus interfering with ingestion and killing by phagocytes.

Transmission. GAS is transmitted via respiratory droplets, usually from a contact with GAS pharyngitis. Occasionally, GAS spreads via contaminated food.

SCARLET FEVER

Scarlet fever (known as scarlatina in older literature references) is a syndrome characterized by exudative pharyngitis, fever, and bright-red exanthem. It is caused by streptococcal pyrogenic exotoxins types A, B, and C produced by group A beta-hemolytic streptococci found in secretions and discharge from the nose, ears, throat, and skin. Scarlet fever may follow streptococcal wound infections or burns, as well as upper respiratory tract infections. Food-borne outbreaks have been reported.

PATHOPHYSIOLOGY

As the name «scarlet fever» implies, an erythematous eruption is associated with a febrile illness. The circulating toxin produced by GAS and often referred to as erythemogenic or erythrogenic toxin causes the pathognomonic rash as a consequence of local production of inflammatory mediators and alteration of the cutaneous cytokine milieu. This results in a sparse inflammatory response and dilatation of blood vessels, leading to the characteristic scarlet color of the rash.

Usually, the sites of GAS replication in scarlet fever are the tonsils and pharynx. Clinically indistinguishable, scarlet fever may follow streptococcal infection of the skin and soft tissue, surgical wounds (i.e., surgical scarlet fever), or the uterus (i.e., puerperal scarlet fever).

EPIDEMIOLOGY

As many as 10 % of the population contracts group A streptococcal pharyngitis. Of this group, as many as 10 % then develop scarlet fever.

In the past century, the number of cases of scarlet fever has remained high, with marked decrease in case-mortality rates secondary to widespread use of antibiotics.

The infection rate increases in overcrowded situations (e.g., schools, institutional settings) and it peaks during late fall, winter, and spring in temperate environments. Immunity, which is type specific, may be induced by a carrier state or overt infection.

Scarlet fever predominantly occurs in children aged 1–10 years, though it can also occur in older children and adults. By the time children are 10 years old, 80 % have developed lifelong protective antibodies against streptococcal pyrogenic exotoxins, which prevent future disease manifestation. Scarlet fever is rare in children younger than 1 year because of the presence of maternal antiexotoxin antibodies and lack of prior sensitization.

Males and females are affected equally. No racial or ethnic predilection is reported for group A streptococcal infection.

CLINICAL FEATURES

The incubation period for scarlet fever ranges from 12 hours to 7 days. Patients are contagious during the acute illness and during the subclinical phase.

The illness generally has a 2 to 7 day incubation period. Its emergence tends to be abrupt, usually heralded by sudden onset of fever associated with sore throat, headache, chills, nausea, myalgias, and malaise. Young children may also present with vomiting, abdominal pain, and seizure. The characteristic rash appears 12–48 hours after the onset of fever.

Fever abates within 12–24 hours after initiation of antibiotic therapy.

A recent history of exposure to another individual with a «strep» infection may aid in the diagnosis.

On day 1 or 2, the ***tongue*** is heavily coated with a white membrane through which edematous red papillae protrude (classic appearance of white strawberry tongue). By day 4 or 5, the white membrane sloughs off, revealing a shiny red tongue with prominent papillae (red strawberry tongue) (figure 6).

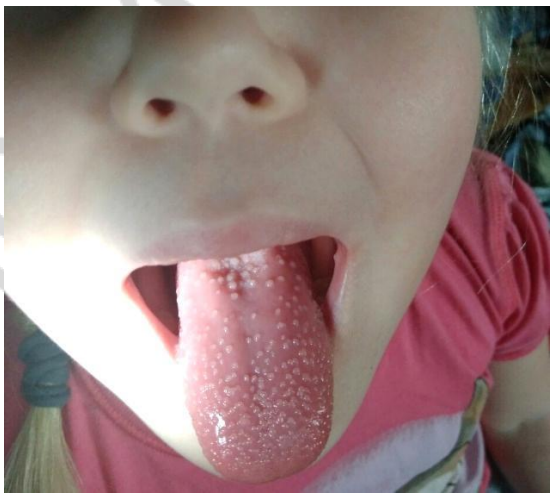

Figure 6. Strawberry tongue

The ***tonsillitis*** typical of scarlet fever (figure 7).

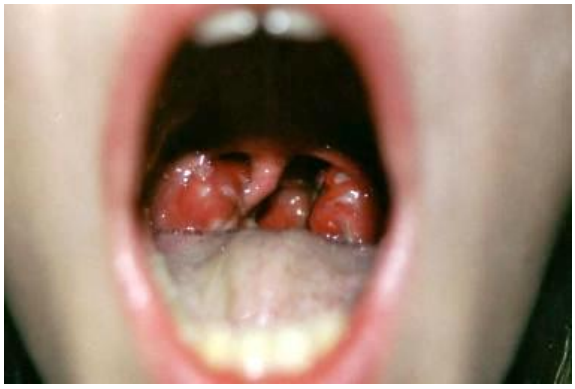

Figure 7. Tonsillitis

Generally, the ***exanthem*** develops 12–48 hours after the onset of fever, first appearing as erythematous patches below the ears and on the neck, chest, and axilla. The characteristic exanthem consists of a fine erythematous punctate eruption that appears within 1–4 days after the onset of the illness. The eruption imparts a dry, rough texture to the skin that is reported to resemble the feel of coarse sandpaper. The erythema blanches with pressure. The skin can be pruritic but usually is not painful. Dissemination to the trunk and extremities occurs over 24 hours. It is usually more prominent in flexural areas (e.g., axillae, popliteal fossae, and inguinal folds). It may also appear more intense at dependent sites and sites of pressure, such as the buttocks. Eventually scarlet macules are seen overlying the generalized erythema («boiled-lobster» appearance).

Capillary fragility is increased, and rupture may occur. Often, transverse areas of hyperpigmentation with linear arrays of petechiae in the axillary, antecubital, and inguinal areas (***Pastia lines***, or the Pastia sign) can be observed. These arrays may persist for 1–2 days after resolution of the generalized rash.

Another distinctive facial finding is a flushed face with circumoral pallor.

The cutaneous rash lasts for 4–5 days, followed by fine desquamation, one of the most distinctive features of scarlet fever. The ***desquamation*** phase begins 7–10 days after resolution of the rash, with flakes peeling from the face. Peeling from the palms and around the fingers occurs about a week later and can last up to a month or longer. The extent and duration of this phase are directly related to the severity of the eruption.

COMPLICATIONS

Complications of scarlet fever may include the following: cervical lymphadenitis, otitis media and/or mastoiditis, ethmoiditis, peritonsillar abscess, sinusitis, bronchopneumonia, meningitis, brain abscess, intracranial venous sinus thrombosis, septicemia, meningitis, osteomyelitis, and septic arthritis, acute renal failure from poststreptococcal glomerulonephritis, hepatitis, vasculitis, uveitis, myocarditis, sepsis with abdominal wall abscess (rarely), invasive group A streptococcal infections and streptococcal toxic shock syndrome (rarely).

Of these, otitis media, pneumonia, septicemia, osteomyelitis, rheumatic fever, and acute glomerulonephritis are the most common. Appropriate evaluation and early intervention with antibiotics are essential to prevent these disorders.

Rare but lethal early toxin-mediated sequelae include myocarditis and toxic shock like syndrome. A lethal form of streptococcal infection is capable of producing the toxic streptococcal syndrome.

Late complications of group A streptococcal infection include acute rheumatic fever and poststreptococcal glomerulonephritis. Risk of acute rheumatic fever following an untreated streptococcal infection has been estimated at 3 % in epidemic situations and approximately 0.3 % in endemic scenarios. Evidence of a recent GAS infection is a prerequisite, yet serologic parameters alone can be difficult to interpret. Acute rheumatic fever occurs 2–3 weeks following initial pharyngitis. According to the revised Jones criteria, the diagnosis of rheumatic fever can be made in the presence of two major criteria (i.e. migrating polyarthritis of the large joints, carditis, subcutaneous nodules, erythema marginatum, Sydenham's chorea) or one major criterion plus two minor criteria (i. e. fever, arthralgia, leucocytosis, ECG abnormalities, a previous episode of rheumatic fever, or inactive heart disease). Chorea and indolent carditis may be isolated findings, indicative of ARF.

Post-streptococcal glomerulonephritis occurs with an estimated incidence of 10–30 new cases per 100, 000 individuals per year, with the highest incidence between 5 and 15 years. It develops about 10–14 days after pharyngitis or, more commonly, a skin infection with a nephritogenic GAS strain. The clinical spectrum varies from asymptomatic microscopic haematuria to acute nephrotic syndrome with frank haematuria, oedema, hypertension, and acute renal failure. If a nephritogenic strain of group A beta-hemolytic streptococci causes infection, the individual has a 10–15 % chance of developing glomerulonephritis. Weeks to months after the illness, transverse grooves (i. e., Beau lines) may appear on the nail plates and hair loss (telogen effluvium) may occur.

PROGNOSIS

When the condition is identified in a timely fashion, the prognosis is excellent. Most patients recover fully after 4–5 days, with resolution of skin symptoms over several weeks. Attacks may recur.

In the preantibiotic era, infections due to GAS were major causes of mortality and morbidity. Historically, scarlet fever resulted in death in 15–20 % of those affected. However, scarlet fever is no longer associated with the deadly epidemics that made it so feared in the 1800s. Since the advent of antibiotic therapy, the mortality rate for scarlet fever has been less than 1 %.

Today, as a result not only of antibiotic therapy but also of enhanced immune status of the population and improved socioeconomic conditions, scarlet fever usually follows a benign course. Any undue morbidity and mortality are more likely to arise from suppurative complications (e.g., peritonsillar abscess, sinusitis,

bronchopneumonia, and meningitis) or problems associated with immune-mediated sequelae, rheumatic fever, or glomerulonephritis. Very rare complications, such as septic shock with multisystem organ failure, have been reported.

DIAGNOSIS

The diagnosis is mostly based on the clinical presentation.

The CBC count commonly reveals a leukocytosis. The WBCs count in scarlet fever may increase to 12, 000–16, 000/μL, with a differential of up to 95 % polymorphonuclear leukocytes. During the second week, eosinophilia, as high as 20 %, can develop.

Urinalysis and liver function tests may reveal changes associated with complications of scarlet fever.

Culture of GAS from normally sterile sites is diagnostic. A specimen should be obtained by vigorous swabbing of a pair of swabs on both tonsils and the posterior pharynx. Throat culture is the gold standard for the diagnosis of acute GAS pharyngitis (sensitivity 90 %–95 %). However, because a 10 %–15 % carriage rate exists among healthy individuals, the presence of GAS is not proof of disease. To maximize sensitivity, proper obtaining of specimens is crucial. Vigorously swab the posterior pharynx, tonsils, and any exudate with a cotton or Dacron swab under strong illumination, avoiding the lips, tongue, and buccal mucosa.

Rapid antigen detection tests are «near-patient tests». Kits are latex agglutination or a costlier ELISA. Rapid antigen detection tests have a specificity of ≥95 % and a sensitivity of 65 %–90 %, yet they may be highly variable in untrained hands.

Serology: anti-streptococcal antibody tests, including anti-streptolysin S and anti-deoxyribonuclease B, are useful in the diagnosis of streptococcal sequelae such as ARF. The antibody response occurs 2–3 weeks after the onset of infection. Serology is not helpful in the diagnosis of acute GAS infection. Single serological testing cannot discriminate between recent or previous infections, and the antibody response may be aborted by antibiotic therapy.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis includes other causes of fever accompanied by erythematous eruptions (appendix 1).

The cutaneous eruption of fifth disease may be confused with that of scarlet fever, but the affected child is usually well and afebrile.

Rubella and measles may appear similar, but the presence of conjunctivitis, purulent rhinitis, and cough are helpful clues to the diagnosis of measles. In addition, the eruption of measles usually begins behind the ears and on the scalp and forehead, not on the torso. Rubella typically begins on the head and face.

Other viral exanthemata, such as those caused by Epstein-Barr virus (infectious mononucleosis), enterovirus, HIV infection may also have to be considered.

Other bacteria-associated syndromes with cutaneous eruptions (e.g., toxic shock syndrome, secondary syphilis) may appear similar to scarlet fever, but the

presence of vasomotor instability, positive serology in the latter should suffice to differentiate them from scarlet fever.

Noninfectious diseases that should be considered include Kawasaki disease, acute lupus erythematosus, morbilliform drug eruption, and juvenile rheumatoid arthritis.

Other problems to be considered include the following:

- atropine toxicity;
- enteroviral infection and nonspecific viral infection;
- pediatric cellulitis;
- plant allergic reactions;
- severe sunburn;
- viral exanthema.

MANAGEMENT AND TREATMENT

Indications for hospital admission:

- severe cases;
- complicated disease;
- additional severe chronic disease;
- epidemiological indication (patient from residential institutions, patient who has siblings from 3 month to 7 years with no history of streptococcal infection, contact adult who work a nurse, primary school teacher, cook, in surgical or obstetric department).

The goals in the treatment of scarlet fever are:

1. to prevent acute rheumatic fever;
2. to reduce the spread of infection;
3. to prevent poststreptococcal glomerulonephritis and suppurative sequelae (e.g., adenitis, mastoiditis, ethmoiditis, abscesses, cellulitis);
4. to shorten the course of illness.

Amoxicillin 40–60 mg/kg/day remains the drug of choice. A I–III generation cephalosporin (cefotaxime 80–100 mg/kg/day, ceftriaxone 50–80 mg/kg/day) may be an effective alternative, as long as the patient does not have any documented anaphylactic reactions to penicillin. A 10- to 14-day course of treatment is usually recommended, and clinical improvement should be noted after 24–48 hours of antibiotic initiation. As alternative, macrolides might be given.

In case of fever, ibuprofen or acetaminophen should be used (table 2). In case of dehydration or severe intoxication, intravenous fluid should be added.

PREVENTION

To minimize contagion, children with scarlet fever should not return to school or daycare until they have completed 24 hours of antibiotic therapy and are clinically improving. Hand hygiene and proper maintenance of environmental hygiene should be highly reinforced.

LONG-TERM MONITORING

After the recovery from scarlet fever, we need to observe the child to reveal possible complications in early stage. On the 7 days after the treatment is finished general practitioner prescribes CBC with differential, urinalysis, ECG if needed. He controls analysis 3 weeks later and in case of good result the observation is finished.

SELF-CONTROL TASK

1. Name the causative agent of measles:

a) Paramyxovirus;
b) β-haemolytic Group A Streptococcus;
c) Herpesvirus;
d) Togavirus;
e) Coxsackievirus.

2. Index of contagiousness in rubella is:

a) 5–10 %;
b) 20–30 %;
c) 75–90 %;
d) 50–85 %;
e) 45–50 %.

3. Describe specific features of rubella rash:

a) small macular rash;
b) predominating localization is on the extensor surfaces of extremities and back;
c) rash elements do not merge;
d) rash disappears during 1–3 days without pigmentation;
e) all the answers are correct.

4. Describe the duration of incubation period in case of scarlet fever:

a) 1–3 days;
b) 2–7 days;
c) 7–14 days;
d) 9–17 days;
e) 11–21 days.

5. Describe the clinical manifestations of measles in the prodromal period:

a) paroxysmal cough with inspiratory whoops;
b) occipital lymphadenopathy;
c) Filatov-Koplic spots;
d) maculopapular exanthema.

6. Which antibiotic should be prescribed in case of scarlet fever:

a) amoxicillin;
b) erythromycin;
c) doxycycline;

d) cefepime;
e) rifampicin.

7. Describe the symptom which is definitely present in typical clinical manifestations of scarlet fever:

a) cough;
b) rash;
c) conjunctivitis;
d) adenoiditis;
e) polylymphadenopathy.

8. The congenital rubella triad is characterized by:

a) congenital kidney defect, lung hypoplasia, polydactylia;
b) congenital heart defect, cataract, sensorineural deafness;
c) sensorineural deafness, polydactylia, strabismus;
d) cataract, strabismus, esophageal atresia.

9. Antibiotic therapy in measles is administered:

a) as etiotropic therapy;
b) as chemoprophylaxis of bacterial infections;
c) in cases of secondary bacterial infections;
d) in cases accompanied by hyperthermia.

10. Name the starting point of rubella and measles vaccination:

a) 3 months;
b) 6 months;
c) 12 months;.
d) 18 months.

Answer key: 1 — a; **2** — c; **3** — e; **4** — b; **5** — c; **6** — a; **7** — b; **8** — b; **9** — c; **10** — c.

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Appendix 1

Differential diagnoses of exanthemous diseases

Disease	Measles	Rubella	Scarlet fever
Incubation period	6–23 days	11–23 days	2–7 days
Onset	Headache, malaise, coryza the 1st day, Koplik's spots the 2nd day, remains through the 3rd, 4th and 5th days. Rash comes out late on the 3rd – 4th day	Little or no malaise, headache, slight catarrhal symptoms, rash is out from 2nd to 3rd day	Acute onset: high fever, symptoms of acute tonsillitis with regional lymphadenitis, sometimes vomiting. Rashes appear within 48 hours
Prodrome	High fever, cough, coryza, conjunctivitis, intoxication which gets stronger within 2–4 days, 3–4 day	Low-grade fever, little or no malaise, headache, slight catarrhal symptoms, 3–5 days	Commonly no or short, malaise, loss of appetite, sore throat, shivering. Lasts from some hours to 1 day
Rash:	Maculopapular rash appears next around 2–4 days later. Generally the more rash, the more unwell the child is. The rash can look almost haemorrhagic	The pink–red maculopapular rash	Confluent erythematous 'sandpaper-like' rash
Size	Medium and big	Small, rarely medium size	Up to 2mm
Occurring order	In stages, first behind the ears, then spreads down the body within 3–4 days	Simultaneously within 1 day appears first on the face and spreads rapidly to the rest of the body	Simultaneously throughout the entire body. The rash usually starts on the head and neck, expands rapidly over the trunk, followed by the extremit
Localization	Depending on the occurring day (1st – face, 2nd – face and trunk, 3rd – face, trunk and extremities)	Throughout the body especially on the axillar skin folds, back, buttocks, and face	Face (red cheeks, circumorial pallor, crimson lips). Intense in skin folds (axillae, cubital, inguinal, popliteal). Pastia's sign. Also on the neck, breast, abdomen, buttocks
Skin tone	None	None	Hyperemia
End stage	Transitions into pigmentation starting from the face	Disappears without within 3–5 days	Leaves no marks, peeling skin, macrolaminar desquamation

Continuation of Appendix 1

Disease	**Measles**	**Rubella**	**Scarlet fever**
Mucous membranes	Filatov-Koplik spots (small 1mm bluish white spots on the buccal mucosa) are present about 1–3 days before the onset of the rash and are characteristic of measles, though not found in all cases	Clean, sometimes singular enanthem spots.	Enanthema and hyperemia on the soft palate, tonsillitis. Strawberry tongue after 4–5 days
Associated symptoms	Conjunctivitis, sever catarrhal symptoms, Filatov-Koplik spots	At all ages, there may be a generalized lymphadenopathy, usually the suboccipital, postauricular, and cervical nodes	Anterior cervical lymphadenopathy, tonsillar exudate, absence of cough. Rash is accompanied by circumoral pallor and strawberry tongue

Appendix 2

The major outbreaks of rubella in 2018 according to the WHO

Country	**Cases**	**% of total**
China	3154	28.7
Indonesia	1215	11.1
India	947	8.6
Ethiopia	682	6.2
Nigeria	486	4.4
Poland	403	3.7
Uganda	398	3.6
Sudan	319	2.9
Yemen	309	2.8
South Africa	305	2.8
Bangladesh	304	2.8
DR Congo	286	2.6
Ukraine	210	1.9
Pakistan	209	1.9
Cote d'Ivoire	175	1.6
Malaysia	154	1.4
Congo	115	1.1
Philippines	111	1

Appendix 3

Skin Rashes: Diseases 1-6*

Number	Other names for the disease	Etiology(ies)
First disease	Rubeola, Measles, Hard measles, 14-day measles, Morbilli	Measles virus
Second disease	Scarlet Fever, Scarlatina	Streptococcus pyogenes
Third disease	Rubella, German measles, 3-day measles	Rubella virus
Fourth disease	Filatow-Dukes' Disease, Staphylococcal Scalded Skin Syndrome, Ritter's disease	Some say the disease does not exist. Others believe it is due to Staphylococcus aureus strains that make epidermolytic (exfoliative) toxin
Fifth disease	Erythema infectiosum	Erythrovirus (Parvovirus B19)
Sixth disease	Exanthem subitum, Roseola infantum, «Sudden Rash», rose rash of infants, 3-day fever	Human Herpes Virus 6B or Human Herpes Virus 7

*The terminology for all but the fifth disease is not used anymore. However, this page could come in handy.

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